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09/805,664	03/13/2001	Judith W. Zyskind	07252-008002	3663

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,664	ZYSKIND ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-93* is/are pending in the application.

4a) Of the above claim(s) *6,7,38-43,51-53,56,81,82 and 88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-37,44-50,54,55,57-80,83-87 and 89-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. Applicant now complies with the requirements for priority and priority is granted to 08/971,090.

Response to Amendment

2. The Declaration filed on December 30, 2002 under 37 CFR 1.131 is sufficient to overcome the Roninson reference.

The declaration persuasively demonstrates prior invention relative to Roninson by the current applicants. However, in view of this newly entered declaration, a new search was performed and Roninson was replaced with Roninson et al as discussed in the rejections below.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-5, 8-22, 24, 26-30, 32, 34-36, 44-50, 54, 55, 57, 58, 61, 63-71, 75, 77-80, 83-87 and 89-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benton et al (U.S. Patent 6,037,123) in view of Roninson et al (U.S. Patent 5,811,234) and further in view of Timberlake et al (U.S. Patent 5,821,076).

Benton teaches a method of screening for an antimicrobial agent (see column 9, line 39 and abstract), comprising the steps:

(a) providing a test compound, an essential gene for proliferation and two samples of a microorganism (see column 255, lines 1-52 and column 9, lines 9-64), (here, for example, the test compounds are the compounds of figure 19, the proliferation gene is the endogenous bacterial proliferation gene NT94 and the two cells are cells with temperature sensitive NT94 and extra wild type copies of NT94)

(b) introducing the microbial proliferation gene into the microorganisms of the first sample (see column 255, lines 1-52) (As noted above, this step is met by the introduction of the wildtype NT94 into the microorganism in the sense orientation)

(c) contacting the test compound with the first sample and second microorganism samples which are viable cells (see column 255, lines 1-52) (The contacting of at least the four compounds of figure 19 is demonstrated),

(d) determining the effect of the test compound on the first and second microorganism samples wherein the test compound is identified as an antimicrobial agent based upon the effect on the gene product where if there is a difference in effect, the compound is identified as antimicrobial (see column 255, lines 1-52 and column 9, lines 9-64)(here a significant inhibition is shown).

Benton further teaches that one effect which can be measured is whether the compound is bacteriostatic and impedes proliferation or is bacteriocidal and kills the cells (also impeding proliferation, necessarily) (column 241, lines 30-67) as well as changes in transcription, metabolism and consequent protein synthesis and rates of translation (column 241, lines 30-67).

Benton teaches analysis of the effect on the polypeptide by immunoassays, enzymatic activity assays which may be direct or indirect (see column 257, lines 42-53).

Benton teaches the use of regulatable promoters (column 241, lines 5-11) including temperature sensitive promoters (column 245).

Benton teaches screening Staph. Aureus, a bacterium which is a gram positive pathogenic bacterium (columns 239-240 and column 255, line 12) as well as Salmonella typhimurium, a gram negative bacterium (column 246, line 21) and Escherichia coli (column 139, line 47).

Benton teaches the use of NT94, which is an exogenous nucleic acid in a plasmid vector that is 925 nucleotides in length and is derived from genomic DNA (see column 139 and 140).

Benton teaches a library of four compounds which compounds are organic (see figure 19) as well as combinatorial libraries (see column 259, line 13).

Benton teaches replica plating (column 249, lines 55-67).

Benton teaches measurement of colony forming units (column 244, lines 1-4).

Benton does not teach a method for identification of microbial proliferation genes by using random fragments.

Roninson teaches a method of screening for genetic suppressor elements which may be targeted at genes essential for cell growth (see column 6, lines 19-25) comprising the steps:

a) introducing a randomly fragmented nucleic acid element which is operably linked to a promoter element which is effective for controlling expression (see column 5, lines 31-54) in either the sense or antisense orientation (column 7, lines 35-43),

b) determination of the effect of the introduced GSE element upon the microorganism compared to the microorganism without the introduced GSE (see column 9, example 3, where control plasmid is used). Roninson further teaches that the screen may be for dominant negative proteins which interfere with normal function (see column 8, lines 49-53). Roninson further teaches the use of fluorescent labels for detection of cells of interest (column 6, lines 11-19). Roninson teaches that the randomly fragmented nucleic acids may be in the range of 350-450 or 600-700 (see

column 9, example 3) and may be sheared or digested (see column 5, lines 30-45). Roninson mentions a variety of organisms of interest (see column 2, lines 32-33).

Timberlake evidences that essential genes are required for proliferation, stating", "Essential survival genes are required for growth (e.g., metabolism, division, or reproduction). Such genes and gene products are useful in developing therapeutic agents such as antifungal, antibacterial, and antiparasitic agents; insecticidal agents; and preventitive antimicrobial agents. Therapeutic agents can reduce or prevent growth, or decrease pathogenicity or virulence, and preferably, kill the organism. The genes and gene products identified by the invention can also be used to develop antimicrobial agents which are effective in preventing microbial infection, e.g., by inhbiting the establishment of a bacterial biofilm, in addition to agents which are useful in the treatment of an established infection (column 2, lines 7-19)".

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the GSE method of Roninson with the antimicrobial screening method of Benton since Benton states "Thus, the invention provides a method of screening for an antibacterial agent by determining the effects of a test compound on the amount or level of activity of a polypeptide gene product of one of the identified essential genes (column 9, lines 22-26)". The ordinary artisan would identify these essential genes using the method of Roninson since Roninson states "The invention provides a general method for obtaining effective genetic suppressor elements (GSEs) for cloned genes or viruses, without extensive structure/function information, and in a simple selection or screening procedure (column 3, lines 46-50)".

Thus, an ordinary practitioner would have been motivated to modify the method of Benton to utilize the randomly fragmented GSE elements of Roninson in screening essential genes since Roninson notes "In another embodiment, suppression is directed against genes that must be expressed in order for cells to grow under specific procedures (see column 6, lines 19-21)." So Roninson can be used to identify the essential genes used by Benton in order to use a simple, rapid and general method to obtain effective. Further motivation to screen for such essential genes is provided by Timberlake who demonstrates that essential genes are excellent targets for therapeutic agents as discusses above.

4. Claims 23, 31, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benton et al (U.S. Patent 6,037,123) in view of Roninson and further in view of Timberlake et al (U.S. Patent 5,821,076) and further in view of Gossen et al (Current Opinion Biotechnology (1994) 5:516-520).

Benton in view of Roninson and further in view of Timberlake teach the method of claims 1-5, 8-22, 24, 26-30, 32, 34-36, 44-50, 54, 55, 57, 58, 61, 63-71, 75, 77-80, 83-87 and 89-93 as discussed above.

Benton in view of Roninson and further in view of Timberlake does not teach the use of all different sorts of inducible promoters.

Gossen teaches the use of inducible promoters under control of outside stimulants (page 516, column 2 to page 517, column 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the gene identification method of Benton

in view of Roninson and further in view of Timberlake with the use of inducible promoters as taught by Gossen since Gossen states "An essential feature of such regulatory systems is the potential to control the activity of a gene in a reversible and temporally defined manner. This will open up new approaches for the analysis of differentiation and developmental processes (page 516, column 1)". An ordinary practitioner would have been motivated to utilize the inducible promoters of Gossen in the gene identification method of Benton in view of Roninson and further in view of Timberlake in order to permit controlled activation of the protein in order to maximize specific effects and minimize non-specific effects of the protein in the analysis of the developmental process of the microbial cells.

5. Claims 25, 33 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benton et al (U.S. Patent 6,037,123) in view of Roninson et al and further in view of Timberlake et al (U.S. Patent 5,821,076) and further in view of Mirabelli et al (U.S. Patent 5,639,595).

Benton in view of Roninson and further in view of Timberlake teach the method of claims 1-5, 8-22, 24, 26-30, 32, 34-36, 44-50, 54, 55, 57, 58, 61, 63-71, 75, 77-80, 83-87 and 89-93 as discussed above.

Benton in view of Roninson and further in view of Timberlake does not teach the use of antisense components in the screening.

Mirabelli teaches screening randomly sheared antisense to identify new drugs and reagents for treatment (see column 6, lines 25-50 and column 8, lines 4-5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the gene identification method of Benton in view of Roninson and further in view of Timberlake with the use of antisense oriented genes since Mirabelli states "The cDNA can then be directionally cloned into the expression vector such that RNAs are produced in an antisense orientation. This approach can identify new genes that are key to successful infection. (column 8, lines 3-6)". An ordinary practitioner would have been motivated to place genes into the antisense orientation to identify essential genes, a desired element of each of Benton, Roninson and Timberlake.

6. Claims 72-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benton et al (U.S. Patent 6,037,123) in view of Roninson et al and further in view of Timberlake et al (U.S. Patent 5,821,076) and further in view of Lam et al (U.S. Patent 5,510,240).

Benton in view of Roninson and further in view of Timberlake teach the method of claims 1-5, 8-22, 24, 26-30, 32, 34-36, 44-50, 54, 55, 57, 58, 61, 63-71, 75, 77-80, 83-87 and 89-93 as discussed above.

Benton in view of Roninson and further in view of Timberlake does not teach test compounds which are inorganic, peptidomimetics, peptides or oligonucleotides.

Lam teaches screening compounds including peptidomimetics, oligonucleotides and peptides (column 6, lines 57-67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the library of Lam with the screening

.method of Benton in view of Roninson and further in view of Timberlake since Lam states "Thus, there is a need in the art for a library of truly random peptide sequences, and oligonucleotide sequences, i.e., bio-oligomer sequences in which a single bio-oligomer species can be readily and quickly isolated from the rest of the library. There is also a need in the art for a method for quickly and inexpensively synthesizing thousands to millions of these truly random bio-oligomer sequences. (column 4, lines 51-57)".)". An ordinary practitioner would have been motivated to utilize the library components of Lam in the gene identification method of Benton in view of Roninson and further in view of Timberlake in order to quickly and inexpensively screen species which are readily isolated from the library and which may have the desired antimicrobial effect.

7. Claims 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Benton et al (U.S. Patent 6,037,123) in view of Roninson et al and further in view of Timberlake et al (U.S. Patent 5,821,076) and further in view of Matsunaga et al (U.S. Patent 4,788,038).

Benton in view of Roninson and further in view of Timberlake teach the method of claims 1-5, 8-22, 24, 26-30, 32, 34-36, 44-50, 54, 55, 57, 58, 61, 63-71, 75, 77-80, 83-87 and 89-93 as discussed above.

Benton in view of Roninson and further in view of Timberlake does not teach measurement of respiratory activity for cell viability.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the respiratory activity measurement of

Matsunaga with the screening method of Benton in view of Roninson and further in view of Timberlake since Matsunaga notes that "The process enables cellular activities such as respiratory activity to be selectively and effectively inhibited and controlled (column 1, lines 32-34). An ordinary practitioner would have recognized that respiratory activity of a cell is an equivalent mechanism for measurement of cell viability to counting colonies since Matsunaga shows that this measures cell viability.

Response to Arguments

8. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

January 29, 2003